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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 08/819,669 | 03/17/1997 | THIERRY BOON | LUD-5253.5-D | 1995 |

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EXAMINER

GAMBEL, PHILLIP

ART UNIT PAPER NUMBER

1644

DATE MAILED: 03/26/2003

44

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/819669

Applicant(s)

BOON

Examiner

GAMBEL

Art Unit

1644

— The MAILING DATE of this communication appears on the cover sheet with the correspondence address —
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 1/6/03
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) _____ is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration:
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) _____ is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment (Paper No. 43), filed 1/6/03, has been entered.
2. Claim 183-191 are pending

Claims 1-182 have been canceled previously.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action. This Office Action will be in response to applicant's arguments, filed 1/6/03 (Paper No. 43). The rejections of record can be found in the previous Office Actions.
4. Upon reconsideration of the file history and applicant's arguments, filed 1/6/03 (Paper No. 43), the previous requirement for the deposit of the biological material for the re-sequencing the 1.7 / 1.8 cDNA molecules disclosed in the specification as filed has been withdrawn.
5. Claims 183-191 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention essentially for the reasons of record and set forth herein.

Applicant's arguments, filed 1/6/03 (Paper No. 43), have been fully considered but are not found convincing.

Applicant asserts that MAGE 1, 2, 3, 4, 5,6 and 7 described in the specification are all encoded by nucleic acid molecules which hybridize to SEQ ID NO: 8. Applicant notes that all of these molecules also satisfy the requirement that they be tumor rejection antigen precursors. Applicant notes that the USPTO has accepted this principle (e.g. see U.S. Patent No. 5,405,940) and that the scientific literature is replete with articles on the molecules and their function as tumor rejection antigen precursors.

Applicant argues that none of the cited cases nor cited art are relevant, given the disclosure of seven species of nucleic acid molecules.

The claims are drawn to an isolated tumor rejection antigen precursor protein, wherein said protein is encoded by a nucleic acid molecule, the complementary sequence of which hybridizes to SEQ ID NO: 8 at 0.1XSSC, 0.1% SDS.

Page 41 of the instant specification that MAGE refers to a family of molecules and that the nucleic acids encoding them share a certain degree of homology and are expressed in tumor cells, including several types of tumor cells. While the family is not restricted to melanoma cells, the family is referred to as MAGE because the first members were identified in human melanoma cells. Further, it is noted that "nucleic acid molecule" refers to all species of DNA, including genomic and complementary DNA (see page 52, paragraph 2 of the instant specification). The tumor rejection antigen precursors are not expressed in most normal adult tissues but are expressed in tumor cells (page 6, paragraph 1 of the specification).

Tumor antigen precursors are processed to form the presentation of tumor rejection antigens (page 2 of the specification), including but not limited to those most characteristic of a particular tumor (page 4 of the specification)

While the nucleic acid set forth in SEQ ID NO: 8 appears to code for the tumor rejection antigen precursor of the MAGE family wherein the tumor rejection antigen precursors are identified in melanoma cells;

The specification discloses in Example 23 (page 19) that MAGE refers to a family of tumor rejection antigen precursor molecules which share a certain degree of homology. Example 25 (page 43) acknowledges that genes encoding MAGE-1,-2 and -3 cross hybridized to a considerable extent.

In contrast to applicant's assertions, the specification does not identify the key structural elements that identify the nucleic acids that encode a tumor rejection precursor antigen. While the specification discloses several species, there is insufficient information concerning identifying the characteristic structural and functional characteristics of nucleic acids which complementary nucleic acids hybridize to SEQ ID NO: 8 under stringent conditions and encode a tumor rejection antigen precursor, in particular a MAGE tumor rejection precursor antigen. Thus, one performing the claimed hybridization would not know that a given nucleic acid encoding an antigen would necessarily be a tumor rejection precursor antigen, in particular a MAGE tumor rejection precursor antigen. It is noted that the designation tumor rejection precursor antigen only specifies where something is expressed, not what is it per se function.

Nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8 do not provide sufficient written description provision of 35 USC 112, first paragraph for a broad genus of diverse tumor rejection antigen precursors.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed tumor antigen precursor and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences.

The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Here, the specification does not provide sufficient written description of a tumor antigen precursors based upon the limited disclosure/recitation of a one nucleic acid encoding MAGE-1 or MAGE tumor rejection precursor antigens that can be isolated from melanoma cells. There is insufficient written description of the structure / sequences of nucleic acids or which the complementary sequence can hybridize to SEQ ID NO: 8 and encode a broad genus of diverse tumor antigen precursors and, in turn, provide the appropriate structural and functional attributes of a myriad of tumor antigen precursors, with distinct structural, expression and functional properties. The claims encompass tumor rejection precursor antigens that are derived from a variety of tumor cells

Further, given the broad variety tumor rejection antigen precursors; there is insufficient written description of the alternative or allelic forms of a tumor antigen precursor encoded by nucleic acids hybridizes to SEQ ID NO: 8 which can be isolated from a wide variety of diverse tumor cell types under the written description provision of 35 USC 112, first paragraph.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that this is a written description rejection rather than an enablement rejection under 35 U.S.C. 112, first paragraph.

Applicant is invited to limit the claimed tumor rejection precursor antigen to a MAGE tumor rejection antigen precursor which are encoded by an isolated nucleic acid ... the complementary sequence of which hybridizes under stringent conditions to SEQ ID NO: 8 wherein said isolated nucleic acid molecule codes for a tumor rejection antigen precursor wherein the tumor rejection antigen precursor can be isolated from melanoma cells.

6. Claims 183-191 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a MAGE tumor rejection antigen precursor which are encoded by an isolated nucleic acid ... the complementary sequence of which hybridizes under stringent conditions to SEQ ID NO: 8 wherein said isolated nucleic acid molecule codes for a tumor rejection antigen precursor wherein the tumor rejection antigen precursor can be isolated from melanoma cells, does not reasonably provide enablement for any "tumor rejection antigen precursor which is encoded by an isolated nucleic acid ... the complementary sequence of which hybridizes under stringent conditions to SEQ ID NO: 8 wherein said isolated nucleic acid molecule codes for a tumor rejection antigen precursor"

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 1/6/03 (Paper No. 43), have been fully considered but are not found convincing.

Applicant argues that the specification has reduced to practice seven species which possess the properties of what is claimed (e.g. MAGE 1, 2, 3, 4, 5, 6 and 7 described in the specification are all encoded by nucleic acid molecules which hybridize to SEQ ID NO: 8).

However, the claims are not limited to MAGE tumor antigen precursor proteins, nor are the claims limited to MAGE tumor antigen precursor proteins isolated from melanoma cells.

While the recitation of "tumor antigen precursor" may have some notion of the properties of the claimed molecule(s), claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make and use the "tumor antigen precursors", commensurate in scope with the claimed invention.

The specification discloses in Example 23 (page 19) that MAGE refers to a family of tumor rejection antigen precursors molecules which share a certain degree of homology. Example 25 (page 43) acknowledges that genes encoding MAGE-1,-2 and -3 cross hybridized to a considerable extent.

In contrast to applicant's assertions, the specification does not identify the key or characteristic structural elements that identify the nucleic acids that encode a MAGE tumor rejection precursor antigen. While the specification discloses several species there is insufficient information concerning the identifying the characteristic structural and functional characteristics of nucleic acids of which complementary nucleic acids hybridize to SEQ ID NO: 8 under stringent conditions encoding a tumor rejection antigen precursor, particularly a MAGE tumor rejection antigen precursor derived from melanoma cells. In order to determine whether a tumor antigen precursor antigen is have the tumor antigen precursor antigen processed by trial and error. The specification has provided a plan or an invitation for the skilled artisan to experiment.

As pointed out previously, the following is noted.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases.

For example, Skolnick et al. (Trends in Biotech. 18:34-39, 2000) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36).

Similarly, Bork (Genome Research 10:398-400, 2000) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399).

Smith et al. (Nature Biotechnology 15:1222-1223, 1997) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene

There is insufficient guidance and direction as to how to make and use the breadth of tumor rejection precursor antigens encoded by nucleic acids encoding tumor antigen precursors by hybridizing complementary sequences to SEQ ID NO: 8 alone; other than that encompassed MAGE tumor rejection precursor antigens encoded by nucleic acids encoding tumor antigen precursors by hybridizing complementary sequences to SEQ ID NO: 8 wherein the MAGE tumor rejection precursor antigen isolated from melanoma cells.

Tumor antigen precursors are processed to form the presentation of tumor rejection antigens (page 6 of the specification), including but not limited to those most characteristic of a particular tumor (page 8 of the specification)

A person of skill in the art is not enabled to make and use the breadth of MAGE tumor rejection antigen precursors, which can be processed to form the presentation of tumor rejection antigens and be characteristic of a particular tumor, commensurate in scope with the claimed invention. The skilled artisan would not predict that all that is required for a tumor antigen precursor is that it can be encoded by a nucleic acid of which the complementary sequence hybridizes to SEQ ID NO: 8. A skilled artisan would expect that other structural and functional attributes would be required to provide for a nucleic acid to encode a MAGE tumor rejection antigen precursor and its ability to be processed to form a tumor rejection antigen characteristic of a particular tumor.

For example, a person of skill in the art could not predict which particular nucleic acids (or amino acid sequences) other than that was set forth in SEQ ID NO: 8 would be sufficient to confer the ability to encode a MAGE tumor rejection antigen precursor and, in turn, wherein the MAGE tumor rejection antigen precursor can be processed to form a tumor rejection antigen characteristic of a particular tumor

The claims are not limited to MAGE tumor rejection antigen precursors isolated from melanoma cells.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, making and using tumor antigen precursors encoded by nucleic acids of which the complementary sequence hybridizes to SEQ ID NO: 8, wherein the appropriate structural and functional features of MAGE tumor rejection antigen precursor would be maintained would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

7. Again, applicant is reminded of the following.

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

The reference to USSN 07/764,364 in the oath appears in error, as this application issued as U.S. Patent No. 5,327,252 directed to a print apparatus.

Application Number 764,364 has the last "4" crossed out and "PCT/US92/04354 / 22 May 1992" has been crossed out.

It is noted that applicant's amendments, filed 6/30/00 (Paper No. 29) and 6/12/01 (Paper No. 38) indicate that applicant will address the defective oath upon allowance.

8. Again, while it is acknowledged that both "BALB/C" and "BALB/c" are used in the literature to describe this mouse strain; applicant is reminded that "BALB/c" is the proper designation of this mouse strain (see pages 27-28).

With respect to applicant's lack of understanding; applicant is invited to amend the specification to disclose the proper designation of this mouse strain in the instant application.

The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected

9. No claim allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
March 24, 2003